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REMARKS

Claims 1-5, 7-27 and 29-34 are currently pending in the above-identified application. Claims 1, 22 and 34 have been amended to recite an "effective immunogenic response" in order to set forth the invention with greater particularity. Support for these amendments can be found, for example, at page 7, lines 27-33, page 8, lines 4-11, page 10, lines 24-28, page 11, lines 23-25, page 12, lines 4-8, page 12, line 24 through page 13, line 6, and throughout the examples. No new matter has been added by these amendments. Applicants respectfully request reconsideration of the claims in the present application in light of the above amendments and the remarks below.

Claim Rejections Under 35 USC §112

Claims 5 and 15 remain rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As previously stated, Applicants will provide a Declaration assuring the public availability of the deposited material when allowed claims have been agreed upon, should the claim language agreed upon require such a declaration.

Claim Rejections Under 35 USC §103

Claims 1-4, 7-14, 16-21 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Midthun *et al.* (*J. Virol.* 1985; 53:949-954), designated Midthun '85, Midthun *et al.* (*J. Clin. Microbiol.* 1986; 24:822-826), designated Midthun '86, Hoshino *et al.* (*J. Med. Virol.* 1997; 51:319-325), and Clark *et al.* (US 6,113,910). As stated in the prior office action and restated in the pending office action the Examiner believes that Clark *et al.* teach a general range of suitable administrative dosages and that the range of disclosed doses is indicative of conventional routine optimization used in the vaccine art for each individual administration including the dosages of less than 10^6 pfu used in the bovine UK rotavirus based compositions claimed in the present invention.

Applicants must again respectfully disagree with the Examiner's summary and analysis of the art of record and the motivation and expectations asserted for the skilled artisan. As stated in Applicants' prior response the Examiner has alleged that the ordinary artisan would have been motivated to optimize the dosage for each patient to reduce detrimental side effects and that a reasonable expectation existed that the compositions of the present invention would not only be immunogenic, but that the compositions would be effective and not possess any detrimental effects. It is the motivation and the level of reasonable expectation asserted in making the present rejection that Applicants do not believe has been supported by the Examiner. Contrary to the position of the Examiner one of skill in the art would not have been motivated to use a dosage of any bovine rotavirus vaccine at less than 10^6 pfu, nor would that artisan have had a reasonable expectation that a dosage of human rotavirus x bovine UK reassortant rotavirus of less than 10^6 would have resulted in an effective immunogenic response.

As summarized in the specification as filed, for example, at page 3, line 25 through page 5, line 8 the results of prior clinical studies with bovine rotavirus and human bovine reassortant vaccine compositions, no bovine rotavirus or human bovine reassortant rotavirus had been successful initiating an effective immune response when used at a dosage below 10^7 pfu much less 10^6 pfu. To summarize briefly, in one clinical trial bovine rotavirus vaccine RIT4237 was administered at a dose range of $10^{7.8}$ to $10^{8.3}$ tissue culture infectious doses₅₀, with the usual dosage exceeding $10^{8.0}$ TCID₅₀. In a separate dose-response study reported by Vesikari and summarized at page 4, lines 1-8 of the specification, the dose of the vaccine composition that resulted in optimal immunogenicity was determined to be in the range of $10^{8.0}$ TCID₅₀. Similarly, in still another study WC3 bovine rotavirus compositions were used in efficacy trials in humans as reported by Clark *et al.*, *Amer. J. Dis. Child.* 140:350-356 (1986). The WC3 strain was administered to infants and young children at a dose range of $10^{7.0}$ to $10^{7.3}$ pfu. This report did not disclose a dosage that would provide significant immunogenicity, but noted that the WC3 strain appeared to possess safety characteristics similar to those of RIT4237, yet was immunogenic at a dose at least five fold less than that used with RIT4237. An estimation of this dosage would suggest that an amount of virus required was well above 10^6 pfu.

Still further, human bovine rotavirus reassortants comprising the bovine WC3 rotavirus strain have been tested in humans. In an efficacy study with a monovalent reassortant of WC3 and a human rotavirus VP7 serotype 1, the reassortant was administered on a three dose schedule to infants and young children at a dosage of $10^{7.3}$ pfu. No efficacy results were reported for this trial. In another efficacy study, a quadrivalent formulation was used which contained three human VP7 reassortants of bovine rotavirus WC3 with a human rotavirus VP7 serotype of 1, 2 or 3 and as a fourth component, a human x bovine reassortant bearing a human rotavirus VP4 protein with the remaining genes derived from the bovine rotavirus WC3. Each of the three VP7 reassortants was used at a dose of $10^{7.0}$ pfu, while the VP4 reassortant was administered at a dosage of 5×10^6 pfu. Immunogenicity data for this trial also was not reported, but these studies indicate that to characteristically produce a protective response similar to that obtained with the rhesus rotavirus or human x rhesus reassortant vaccines a dosage of 10^7 to $10^{8.3}$ was required (Clark *et al.*, *Arch Virol.* (suppl.)12:187-198 (1996); Vesikari *et al.*, *Arch. Virol.* (suppl.)12:177-186 (1996)). This dosage is 10 to 100 times that for the rhesus rotavirus and human x rhesus reassortant vaccine compositions and the compositions of the present invention. In another yet another study, Clark *et al.*, *Vaccine* 4:25-31 (1986), a NCDV x human WA rotavirus strain was administered orally at a dosage of up to 10^6 pfu in adults, but these compositions were as summarized in the abstract of the paper as "relatively ineffective in eliciting a serum antibody response."

The reported results of these prior trials with other bovine rotavirus and human x bovine rotavirus reassortant compositions summarized above and in the present application as originally filed, do not provide motivation to one of skill in the art to pursue compositions comprising less than $10^{6.0}$ pfu of each human x bovine UK rotavirus reassortant. Instead the prior art teaches that others had failed to obtain effective immunogenic composition with other bovine rotavirus strains when the virus was used at a concentration of less than about 10^7 pfu. Therefore, Applicants do not believe that the compositions of the present invention are merely indicative of conventional routine optimization used in the vaccine art as asserted by the Examiner because compositions comprising such a low amount of rotavirus would not be

expected to possess sufficient immunogenicity to be effective. In particular, there is no evidence in the prior art suggesting to the skilled artisan that a composition comprising less than 10^6 pfu of a human bovine reassortant based on the bovine UK strain would provide an effective immunogenic composition. Claim 1 has also been amended to recite the term "effective immunogenicity" to clearly set forth this particular characteristic of the invention.

The Midthun *et al.* references and Hoshino *et al.* cited by the Examiner add nothing to the disclosure of Clark *et al.* to suggest that a human bovine UK reassortant rotavirus could have been successfully used at a dosage of less than 10^6 pfu. As argued previously, the disclosure of "the Midthun references describing the neutralization of the rotavirus constructs with monoclonal antibodies to each VP7 human glycoprotein" relates to the process for selection of the rotavirus reassortants having the desired VP7 antigen. The disclosed process for selecting the desired VP7 serotype reassortant has no predictive value as to the effective immunogenicity of the rotavirus reassortant when administered to an individual. Hoshino *et al.* disclosing the four clinically important serotypes of rotavirus and/or Clark *et al.* disclosing "a vaccine composition comprising multiple rotavirus reassortants" based on the bovine WC3 bovine rotavirus strain and its derivatives does nothing to provide the skilled artisan with any expectation regarding the use any human bovine UK reassortant rotavirus composition at a dosage of less than 10^6 pfu as an effective immunogen. The prior disclosures relate to bovine and human x bovine rotavirus reassortant vaccine compositions based on bovine rotavirus other than the bovine UK that require dosages 10 to 100 times the dosages of the compositions disclosed in the present application that provide an immunogenically effective composition. The prior disclosures do not disclose or suggest the present invention, but would instead teach away from the compositions and methods claimed in the present application.

Based on the above amendments and remarks the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1-4, 7-14 and 16-21 under 35 U.S.C. § 103(a) as unpatentable over Midthun *et al.* (*J. Virol.* 1985; 53:949-954), designated Midthun '85, Midthun *et al.* (*J. Clin. Microbiol.* 1986; 24:822-826), designated Midthun '86, Hoshino *et al.* (*J. Med. Virol.* 1997; 51:319-325), and Clark *et al.* (US 6,113,910).

Claims 22-34 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Hoshino *et al.* (*J. Med. Virol.* 51:319-325, 1997) and Clark *et al.* (US 6,113,910) for the reasons of record for claims 22-33. The Examiner has also included claim 34 in this rejection because the claim encompasses the limitations of claims 22-33. The Applicants' comments regarding the citation of the Hoshino *et al.* reference as rendering Claims 22-33 *prima facie* obvious have been summarized by the Examiner as being based on "the reference teaches double reassortant mutants and does not indicate that an immune response elicited in guinea pigs would be immunogenic in humans." The Examiner continues that the number of bovine genes within the reassortant virus is not a limitation of the claims and that therefore the reassortants of Hoshino *et al.* meet the claim limitations of possessing at least four VP7 serotypes. Further, the Examiner states that Applicants have not provided any evidence that would refute the use of the rotavirus art-recognized animal model demonstrated by the teachings of Hoshino *et al.*

Applicants again must strongly disagree with the analysis of the Examiner. It is not the argument of Applicants that the Hoshino *et al.* reference is deficient because it teaches double mutants administered to a guinea pig animal model, but that the teachings of the reference are not directed to an art-recognized animal model of vaccine efficacy. Hoshino *et al.* teach the construction of certain human bovine rotavirus reassortants. These reassortants were administered to guinea pigs to produce hyperimmunized animals. In administering the reassortant rotavirus to the animals the antigen is provided in an amount and at a frequency that is intended to produce an immune response to both highly immunogenic and weakly immunogenic antigens in the rotavirus preparation. The immunogenicity data produced in any hyperimmunized animal model can not be extrapolated to determine the immunogenicity of any composition in a human regardless of the antigen used. Hyperimmunization, as defined in Stedman's Medical Dictionary, 27th Edition, Lippincott Williams & Wilkins, Philadelphia 2000, page 850, (attached for the convenience of the Examiner) as "the induction of a heightened state of immunity by the administration of repeated doses of antigen." The studies reported by Hoshino *et al.* characterize the antigenicity of the reassortant rotaviruses not to characterize the safety, immunogenicity, as well as protective efficacy in humans, but to determine which

antigens in the reassortant rotavirus compositions induced neutralizing antibodies. In addition, the authors draw no conclusions from the guinea pig data as to the possible immunogenicity of the compositions and instead indicate evaluation of the safety, immunogenicity and protective efficacy of the compositions would be carried out later. See Hoshino *et al.*, page 323, right column, lines 31-35.

Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 22-34 under 35 U.S.C. § 103(a) as being unpatentable over Hoshino *et al.* and Clark *et al.* in view of the above amendments and remarks.

CONCLUSION

Applicants respectfully request reexamination and reconsideration of the pending claims. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 30 June 2004

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hy-per-he-mo-glo-bi-ne-mia (hī'per-hē'mō-glō-bi-nē'mmē-ā). An unusually large amount of hemoglobin in the circulating blood plasma; i.e., much more than that ordinarily observed in most examples of hemoglobinemia.

hy-per-hep-a-ri-ne-mia (hī'per-hep'ar-in-ē'mē-ā) [MIM* 144050]. Elevated plasma concentrations of heparin; believed to be the cause of a heritable bleeding tendency; probably autosomal dominant inheritance.

hy-per-hi-dro-sis (hī'per-hī-drō'sis). Excessive or profuse sweating. SYN polyhidrosis, sudorrea. [hyper- + hidrosis]

gustatory h., excessive sweating of the lips, nose, and forehead after eating certain foods; it is physiologic in many persons, but sometimes occurs after parotid surgery or as a result of damage to the parasympathetic or sympathetic nerves of the head and neck.

hy-per-hy-dra-tion (hī'per-hī-drā'shūn). Excess water content of the body; may result from the intravenous administration of unduly large amounts of glucose solution. SYN overhydration.

hy-per-hy-dro-chlo-ria (hī'per-hī-drō-klōr'ē-ā). SYN hyperchlorhydria.

hy-per-hy-dro-chlo-ri-d-i-a (hī'per-hī-drō-klōr-id-ē-ā). Excessive acid secretion by the stomach; associated with peptic ulcer disease. [hyper- + hydrochloric, acid + -ia]

hy-per-hy-dro-pe-xy, **hy-per-hy-dro-pex-is** (hī'per-hī-drō-pek-sē, hī'per-hī-drō-pek'sis). Increased fixation of water in tissues. [hyper- + G. *hydōr*, water, + *pēgnymi*, to fasten]

hy-per-hy-drox-y-pro-line-mia (hī'per-hī-drōk'sē-prō-lēn-ē-mē-ā). SEE hydroxyprolinemia.

hy-per-im-i-do-di-pep-ti-du-ria (hī'per-im'i-dō-dī-pep'tid-oor-ē-ā). Elevated levels of imidodipeptides (e.g., Xaa-Pro) in the urine; due to a deficiency of prolidase.

hy-per-im-mune (hī'per-im-mūn'). Having large quantities of specific antibodies in the serum from repeated immunizations or infections.

hy-per-im-mu-ni-ty (hī'per-i-mū-ni-tē). A high degree of immunity.

hy-per-im-mu-ni-za-tion (hī'per-im-oo-nī-zāshūn). 1. The induction of a heightened state of immunity by the administration of repeated doses of antigen, often used in allergy desensitization. 2. Passively acquired immunity by the injection of hyperimmune gamma globulin.

hy-per-in-di-can-e-mia (hī'per-in'di-kan-ē'mē-ā). An unusually large amount of indican in the circulating blood; i.e., greater than that observed in most instances of indicanemia.

hy-per-in-fec-tion (hī'per-in-fek'shūn). Infection by very large numbers of organisms as a result of immunologic deficiency. Cf. superinfection.

hyperinflation (hī'per-in-flā'shūn). Overdistention of airways and alveoli, sometimes leading to emphysema, caused by obstructive lung disease; occurs reversibly with asthma, and can occur locally with aspiration of a foreign body with a subsequent ball-valve phenomenon. [hyper- + inflation]

hy-per-i-no-se-mia (hī'per-i'nō-sē'mē-ā, hī'per-in'ō-). A greatly increased quantity of fibrinogen in the circulating blood; under certain conditions, unusually large amounts of fibrin may be formed, thereby resulting in a greater degree of coagulability of the blood. SYN hyperinosis. [hyper- + G. *is* (in-), fiber, + *haima*, blood]

hy-per-i-no-sis (hī'per-i'nō'sis). SYN hyperinosemia.

hy-per-in-su-li-ne-mia (hī'per-in'soo-lin-ē'mē-ā). SYN hyperinsulinism.

hy-per-in-su-lin-ism (hī'per-in'soo-lin-izm). Increased levels of insulin in the plasma due to increased secretion of insulin by the beta cells of the pancreatic islets; decreased hepatic removal of insulin is a cause in some patients, although h. usually is associated with insulin resistance and is commonly found in obesity in association with varying degrees of hyperglycemia. SYN hyperinsulinemia.

alimentary h., elevated levels of insulin in the plasma following ingestion of meals by individuals with abnormally rapid gastric emptying (e.g., following gastroenterostomy or vagotomy); rapid

glucose absorption leads to excessive insulin release which in turn can lead to a marked fall in blood glucose to hypoglycemic levels.

hy-per-in-vo-lu-tion (hī'per-in'vō-loo'shūn). SYN superinvolution.

hy-per-i-so-ton-ic (hī'per-i-sō-ton'ik). SYN hypertonic.

hy-per-ka-le-mia (hī'per-kā-lē'mē-ā). A greater than normal concentration of potassium ions in the circulating blood. SYN hyperkalemia, hyperpotasemia. [hyper- + Mod. L. *kalium*, potash, + G. *haima*, blood]

hy-per-kal-i-e-mia (hī'per-kal-i-ē'mē-ā). SYN hyperkalemia.

hy-per-kal-u-re-sis (hī'per-kal-ū-rē'sis). Excessive urinary excretion of potassium. [hyper- + Mod. L. *kalium*, potassium, + G. *oureō*, to urinate]

hy-per-ker-a-tin-i-za-tion (hī'per-ker'at-i-ni-zā'shūn). SYN hyperkeratosis.

hy-per-ker-a-to-sis (hī'per-ker-ā-tō'sis). Thickening of the horny layer of the epidermis or mucous membrane. SEE ALSO keratoderma, keratosis. SYN hyperkeratinization.

h. congen'ita, SYN *ichthyosis vulgaris*.

diffuse h. of palms and soles, an autosomal dominant disorder with onset in early infancy; characterized by hyperkeratotic, scaling plaques and often hyperhidrosis on the palms and soles. SYN Unna-Thost syndrome.

epidermolytic h. [MIM*144200], characterized by localized lesions, keratosis palmaris and plantaris, and elevated IgE, associated with hyperkeratosis, hypergranulosis, and reticular degeneration in the upper epidermis; autosomal dominant inheritance, caused by mutation in the epidermolytic palmoplantar keratoderma gene (EPPK) on chromosome 17q. Generalized epidermolytic h. is present in bullous congenital ichthyosiform erythroderma. SYN porcupine skin.

h. follicula'ris et para-follicula'ris, discrete and confluent horny follicular plugs on a crateriform base, often occurring on the arms and legs in diabetics with renal failure; possibly a severe form of perforating folliculitis. SEE ALSO perforating folliculitis. SYN Kyrle disease.

generalized epidermolytic h., SYN bullous congenital ichthyosiform erythroderma.

h. lentacula'ris per'stans [MIM*144150], small hyperkeratotic papules on the dorsa of the feet and legs and occasionally elsewhere, with pinpoint keratotic papules of the palms and soles; onset in the third and fourth decades; an autosomal dominant trait. SYN Flegel disease.

hy-per-ke-to-ne-mia (hī'per-kē'tō-nē'mē-ā). Elevated concentrations of ketone bodies in the blood.

hy-per-ke-ton-u-ria (hī'per-kē'tō-noo'rē-ā). Increased urinary excretion of ketonic compounds.

hy-per-ki-ne-mia (hī'per-ki-nē'mē-ā). Increased circulation rate; increased volume flow through the circulation; supernormal cardiac output. [hyper- + G. *kineō*, to move, + *haima*, blood]

hy-per-ki-ne-sis, **hy-per-ki-ne-sia** (hī'per-ki-nē'sis, -nē'zē-ā). 1. Excessive motility. 2. Excessive muscular activity. SYN hypercinesia, hypercinesia, supermotility. [hyper- + G. *kinēsis*, motion]

hy-per-ki-net-ic (hī'per-ki-net'ik). Pertaining to or characterized by hyperkinesia.

hy-per-lac-ta-tion (hī'per-lak-tā'shūn). SYN superlactation.

hy-per-leu-ko-cy-to-sis (hī'per-loo'kō-sī-tō'sis). An unusually great increase in the number and proportion of leukocytes in the circulating blood or the tissues; i.e., much more than that ordinarily observed in most instances of leukocytosis.

hy-per-lex-ia (hī'per-lek'sē-ā). In mentally retarded children, the presence of relatively advanced reading ability. [hyper- + G. *lexis*, word, phrase]

hy-per-li-pe-mia (hī'per-li-pē'mē-ā). Elevated levels of lipids in the blood plasma. There are several types of h. One is associated with a deficiency of δ -aminoadipic semialdehyde synthase. SEE ALSO lipemia.

carbohydrate-induced h., SYN type III familial hyperlipoproteinemia, type IV familial hyperlipoproteinemia.

combined fat- and carbohydrate-induced h., SYN type V familial hyperlipoproteinemia.

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Database design by Lexi-Comp Inc., Hudson, OH

Printed in the United States of America by World Color, Inc.

Library of Congress Cataloging-in-Publication Data

Stedman, Thomas Lathrop, 1853-1938.

Stedman's medical dictionary.—27th ed.

p.; cm.

ISBN 0-683-40007-X (regular)—ISBN 0-683-40008-8 (deluxe)

1. Medicine—Dictionaries. I. Title: Medical dictionary. II. Title.

[DNLM: 1. Medicine—Dictionary—English. W 13 S812m 1999]

R121 .S8 1999

610'.3—dc21

99-056094

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1 2 3 4 5